Title:
PARTICIPATION IN BIOBANKS **FOR RESEARCH** BY INCAPACITATED ADULTS. REVIEW AND **DISCUSSION** OF CURRENT GUIDELINES.

Running Head:
Participation in biobanks by incapacitated adults.

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ABSTRACT

Objective

Biobanks **for research** and genetic research are important opportunities to create new understanding of complex disorders, such as psychiatric disorders and dementia. The management of biobanks for subjects with psychiatric disorders or dementia raises additional challenges due to the ethical issues regarding the potentially impaired decision-making capacities of the subjects. The aim of this paper is to study i) how guidelines address the matter and ii) how they can be implemented in real research situations with patients suffering from psychiatric disorders and dementia.

Method

We collected and analysed all the relevant guidelines and position papers from national and international organizations dealing with research on biological materials and selected documents mentioning the participation of incapacitated adults in genetic research and biobanks.

Results

Eighteen of the 30 analysed documents contain explicit references to adults who are unable to give consent. The main topics addressed by the guidelines are the following: i) informed consent, ii) principles of non-therapeutic research and iii) ethics committee (EC) review.

Conclusions

In biomedical research, guidelines are an important instrument for facilitating research while promoting subjects' rights and wellbeing. Compared to legally binding documents, guidelines are more flexible and can be more easily revised according to evolving research situations **and for adaptation to real persons and** research settings. We suggest measures to implement the **analyzed guidelines taking into consideration** the case for the participation of patients with

neuropsychiatric disorders, who can have impairment of decision-making capacities without being obviously incompetent, in genetic research and biobanks.

BACKGROUND

Genetic research and research on biological materials are rapidly increasing and are generally regarded as a powerful way of producing new knowledge and possibilities for treatment. Indeed, human biological materials may provide relevant information on the genesis and evolution of diseases and will hopefully contribute to the future development of treatments and drugs (Wolf, 2010).

Research on biological materials is on-going in multiple fields, including psychiatric disorders and dementia, and aims, mainly, to discover correlations between genetic factors and disease onset and evolution and to understand individual patients' responses to pharmacological treatments.

The possibility of conducting research on biological materials in an effective manner depends on the availability of a large number of samples and the ability to perform future studies on the same samples, which cannot be planned at the time of their collection.

In this context, biobanks, which aim to collect and store biological samples on a large scale, play a key role and have great value. The creation and management of biobanks nevertheless raises ethical and legal issues concerning informed consent, ownership of the samples, data confidentiality, access to the biobank, banning of the commercial exploitation of biological materials and discriminatory use of the results (Gottweis and Lauss, 2010; Hansson, 2009; Cambon-Thomsen *et al.*, 2007; Zika *et al.*, 2008).

The participation of patients affected by neuropsychiatric disorders in genetic research and in the creation of biobanks presents additional specific challenges, as they may lack the ability to fully understand and appreciate the significance and implications of their participation in research (Knoppers *et al*., 2002; Olde Rikkert *et al.*, 2008; Kim *et al.*, 2002; van der Vorm *et al.*, 2008).

The circumstance that information regarding biobanks and future studies on biological materials **as well as the secondary use for research purposes of biological materials taken for clinical reasons,** is particularly complex and inevitably less specific than in other kinds of research may further complicate the picture.

A number of national and international guidelines and position papers dealing with biobanks and genetic research address the issue of the participation of adults who are not able to give consent. We selected such papers and guidelines with the aims of analysing how **they** address the matter and discussing how **they** can be implemented in real situations in which patients suffering from conditions, such as some of the more severe mental illnesses and the early stages of dementia that can impair decision-making capacities without rendering subjects obviously incompetent to make decisions (Appelbaum and Grisso, 2001), participate in research.

REVIEW OF GUIDELINES

Data collection

We analysed 28 guidelines and position papers dealing with research on biological materials that were previously studied in a systematic review of genetics research on minors conducted in the context of the GeneBanC project (Hens *et al.*, 2009). **For that review MedLine, Embase and Google Scholar were used as a primary source of information to identify relevant literature as well as official websites of ethical committees, professional organizations and regulating bodies from the US and the European Union. The review focused on documents about genetic databases (so-called biobanks) and about stored biological samples that mentioned genetic research. Documents discussing archived human tissue without mentioning genetic research**

were discarded. General documents on genetic research were preserved, as long as they at least mention banking of data. Only documents no older than 1990 were preserved, and legally binding documents were not included.

To find relevant guidelines published after that review, we used MedLine and Google Scholar as primary sources of information using the following keywords: "biobanks", "research on biological samples", and "genetic research". Our focus was guidelines and recommendations, and therefore we did not take legally binding documents into consideration. Only guidelines available in English or French were used. The search was updated in November 2012 and resulted in the inclusion of the OECD guidelines (29) and the opinion of the German Ethics Council (30) in the present review.

Review Results

Eighteen of the 30 documents analysed **(list provided below)** contained explicit references to adults who are unable to give consent **(Tab 1).**

The expressions used in the documents to identify those subjects are different: incompetent (1, 13) mentally incompetent (3), unable to give consent (5, 8, 10, 27), incapable or not capable of giving consent (17, 18, 20, 21, 26), incapable of discernment (25) incapacitated (13, **16,** 19, 22) and without capacity to consent (14, 21, 29). **Even though these wordings may be used with different meanings in different contexts (legal or medical), in the guidelines they all are used to indicate people who are regarded as not able to give consent for conditions that impair their decision making capacities. The present paper reflect this use of the terms. The above** expressions are employed for both minors and adults; in the former case, the incapacity depends on the person's age, while in the latter case, the incapacity is due to disability or disease. **In addition, the ESHG Recommendation (7) refers more generally to "vulnerable subjects".**

TABLE 1

The main topics taken into account regarding incapacitated adults are the following: i) informed consent, ii) principles of non-therapeutic research and iii) ethics committee (EC) review **(Tab 2).**

Consent

In the area of consent, the core themes are the following: 1) who should give consent for donation/removal of tissues from an incapacitated person for biomedical research; 2) how the person acting on behalf of the incapacitated person should act; and 3) what the role of the incapacitated person **is** in the consent process.

Who should give consent. When a donor or research subject is not fully able to give valid consent, nearly all guidelines [**14**] require the involvement/intervention of a third person who should represent the incapacitated adult and is variously defined as a legally authorised representative (3, 10, 21, 26, 27), legal representative (18, 21, 25), carer or relative (8), trustworthy person (17), guardian (19, 22, 27), legal proxy (13), personne qui représente la personne inapte: tuteur, curateur ou mandataire (16), or a person or organization who can legally give consent (5).

Almost all documents [**12**] ask for a representative who must be identified in accordance with the applicable law and thereby attribute this authority to the national legislator. Reference to a person who does not need to be determined in accordance with the domestic law is quite uncommon; this case is present in only two guidelines (**17, 8**). The National Consultative Ethics Committee for Health and Life Sciences states that, in situations in which consent cannot be directly provided by the person concerned, “some trustworthy person is consulted instead, either a relative or someone who has been designated”. The Medical Research Council (2001) states that, to involve adults in research who cannot give valid consent, “the agreement of carers or relatives must be sought” despite the fact that “there is no provision in English law for anyone to give consent on

behalf of another". The carer became the legal representative through the subsequent Mental Capacity Act (2005) that deals, *inter alia,* with the consent of incapacitated people in biomedical research. According to the Act, a person who "otherwise than in a professional capacity or for remuneration, is engaged in caring for P [i.e. the person who lacks capacity] or is interested in P's welfare" has to be consulted.

With regard to the wording used to describe the involvement of the third person in the consent process, the guidelines mainly refer to the representative's consent as a substitute for the consent of a non-competent person (i.e., consent should be given by the representative) (3, 5, 19, 21, 22, 26). Different wordings are used by the CIOMS, which requires that "permission is obtained from a responsible family member or a legally authorized representative in accordance with applicable law" (10); by the MRC, which asks for the "agreement of carers or relatives"(8); and by the French National Consultative Ethics Committee for Health and Life Sciences, which states that "some trustworthy person is consulted instead" (17).

How the representative should act. Few guidelines outline the factors that need to be taken into account by the representative when he/she is expressing consent on behalf of the patient. The interest of the incapacitated person is the major criterion mentioned in the analysed documents. The best interest of the person concerned is mentioned as principle for acting (7), as an element the representative should have regard to (18), as something that needs to be properly safeguarded (8, 17), and as the basis of special protective measures to be put in place for vulnerable persons (20).

Although they are not expressly addressed to the representative, three guidelines (21, 26, 27) point out the natural and previous wishes of the person lacking his/her capacity as a criterion that should be followed when adults not able to consent are involved. According to the Nationaler

Ethikrat, **"**Their [people who lack the capacity to give consent] natural wishes must be taken into account in every case". In similar terms, the Austrian Bioethics Commission states that "the natural will of a subject who is incapable of giving consent must be respected", and the European Nutrigenomics Organisation (NuGO) affirms that "If the volunteer is an incapable adult, possible previously expressed wishes or objections should be considered".

Finally, the American Medical Association mentions a different criterion that states that the representative's consent has to be given "under circumstances in which informed and prudent adults would reasonably be expected to volunteer themselves or their children" (3).

What the role of the incompetent person **is.** Another major theme in the studied documents is the role of the non-competent person in the consent process. Even if the incapacitated adult cannot express fully valid consent to the removal of biological materials or to the research, that does not mean he/she is excluded from the decision process.

As far as possible, the consent of the incapacitated must be sought in relation to his/her capacities (10, 16, 22), and "appropriate means of communication must be used or, as the case may be, developed" (21). In addition, according to the German Nationaler Ethikrat, subjects have the right to be informed "on the use of their samples and data and on findings accruing from the research", avoiding that the person without the capacity to give consent was confronted with "genetic findings from research on his samples and data that have no direct therapeutic and diagnostic relevance to him" (21).

Furthermore, objections or the refusal of the research subject (1, 10, 16, 21, 26, 27) and his/her natural or previously expressed wishes (21, 26, 27) should be respected. An exception to the duty to follow a subject's prospective refusal is stated in the CIOMS guidelines in the event "there is no reasonable medical alternative and the local law permits overriding the objection" (10). In this

regards, it should be noted that CIOMS ethical guidelines are intended for biomedical research *tout court* and not with specific regard to genetic research: indeed, it seems difficult to apply the criterion of "no medical alternative" to non-therapeutic research. Only the document issued by the Human Genetic Commission makes reference to "a functional test" that must be performed to determine which questions and aspects the person is able to agree to (14) and thereby stresses that the capacity has to be assessed, not in general terms, but in relation to a specific decision.

Principles of non-therapeutic research

The second issue taken into consideration in the guidelines refers to the principles of non-therapeutic research with incapacitated adults. In particular, in application of these principles, research should not be conducted unless the following conditions are met: 1) the risk is minimal; 2) there is a benefit for others with the same disease; 3) there is a benefit for the participant; and 4) investigation cannot be undertaken with competent adults (knowledge cannot be otherwise obtained).

Minimal risk. Minimal risk is one of the principles of non-therapeutic research variously mentioned in six documents. The UK Nuffield Council on Bioethics, the Medical Research Council and the Irish Council for Bioethics state that the risk must be "negligible" (1, 8, 22) and the research procedures "not unduly invasive" (1, 22), while the WHO and the Nationaler Ethikrat use the expression "minimal risk" (19, 21).

Only CIOMS guidelines offer a notion of the risk that research with individuals incapable of giving consent should entail when there is no prospect of direct benefit for the person concerned: the risk should be "no more likely and not greater than the risk attached to routine medical or psychological examination of such persons" (10). The WHO (19), stating that risk must be minimal

for the use of samples or information from vulnerable people, makes overt references to the Declaration of Helsinki and CIOMS guidelines: “The use of samples or information from vulnerable groups, such as children or incapacitated adults must be subject to the same internationally agreed guidelines for research as embodied in instruments such as the Council for the International Organizations of Medical Sciences, International Ethical Guidelines for Biomedical Research Involving Human Subjects (1993) and the Declaration of Helsinki (2000)”.

The Nationaler Ethikrat (21) quotes different views on acceptable risk that exist in the literature without taking a position: on one side are those who argue that “given a low level of risk, the involvement of subjects lacking the capacity to give consent may be contemplated if the research concerned is intended to benefit others affected by the same disease […] At any rate, those incapable of giving their consent ought not to be exposed to any non-minimal risks (whether physical or psychological) or stresses for the purposes of research carried out for the benefit of others”; on the other side are those who state that “it is not readily, if at all, possible to determine whether risks and stresses are in fact minimal [...] In view of the particular protection needs of those incapable of giving their consent, verifiable criteria and methods for the definition of minimal risks should be developed”.

Benefit for others. To permit research with incapacitated people, some guidelines refer to the principle of benefit for others, namely for other people with the same condition/disease (10, 16, 19, 21, 22). The Nationaler Ethikrat (21) reports that the questions of when and under what conditions it is possible to consider research for the benefit of others legitimate are hotly disputed in the literature; nevertheless, the Committee does not formulate a proposal on this point.

Benefit for the participant. A third principle that asks research on subjects who cannot consent be carried out if there is any direct benefit to participants, is quoted by five guidelines (8, 10, 16, 19,

21). The Nationaler Ethikrat (21), while states that the debate on research with incompetent adults for the benefit of others is still open, asserts as not disputable the fact that people not fully able to give consent may be involved in research that is likely to be beneficial to participants themselves.

Knowledge cannot be otherwise obtained. Four guidelines refer to the fourth principle of research on incapacitated adults by explicitly outlining that incapacitated adults should be included in research only if that research cannot be undertaken with competent adults (1, 3, 10) or if relevant knowledge cannot be obtained otherwise (1, 22).

Ethics committee's review

Six of the above mentioned guidelines explicitly refer to ethics committees' opinions when incapacitated adults are involved in the research (1, 8, 10, 13, 20, 26). Seven other guidelines recommend the approval of the ethics committee for research projects using human biological samples (7, 14, 21, 22, 27) or genetic data (5, 19), either in general terms or for specific situations, and indirectly also require the ethics committee's opinion on the event of the involvement of incapacitated adults.

The Nuffield Council on Bioethics indicates the EC approval as an additional safeguard (1), while the Austrian Bioethics Commission and the Germany Society of Human Genetics require respectively the intervention of the ethics committee "for the approval of the research project" (26) and "before the use of biological material" to assess if the ratio of risk and benefit is appropriate (20). In the Singapore's Statement on Human Tissue Research, the involvement of the ethics committee is needed along with the review of a legal advisor (13). CIOMS guidelines identify the EC's approval, along with an overriding scientific or medical rationale, as the necessary

conditions to allow an increase from minimal risk when incapable adults are subjects of research (10). Finally, the Medical Research Council states that the informed independent person who should ensure that the incapacitated person's interests and welfare are protected has to be "acceptable to the local ethics committee"(8).

TABLE 2

DISCUSSION OF CURRENT GUIDELINES FOCUSING ON RESEARCH INVOLVING SUBJECTS WITH NEUROPSYCHIATRIC DISORDERS

In biomedical research, guidelines and position papers are an important instrument for facilitating research while at the same time promoting subjects' rights and wellbeing. Compared to legally binding documents, guidelines are more flexible and can be more easily revised according to evolving research situations **and to the concrete persons and research settings. They are suitable to cover as ethical guidance areas that are not regulated by legal documents either because of the novelty of the matter or because strict legal regulation is not regarded as a solution. Finally, even though guidelines operate within the existing legal framework and need to be read in the light of the existing law, they may challenge legal regulations and open democratic discussion on interested topics. In comparison with individual opinions, guidelines reflect a perspective that is shared by a large group of people: this gives them more authority than individual views. We selected guidelines and position papers dealing with biobanks and genetic research addressing the issue of the participation of adults not able to give consent, with the aim of analyzing how they address the matter and discussing how they can be adapted** for the participation of patients with neuropsychiatric disorders, who can have impairment of decision-making capacities without being obviously incompetent, in genetic research and biobanks.

The judgment of incompetence

The analysed guidelines agree that – as a general rule- the collection and use of human biological materials for research purposes requires the informed consent of the person concerned and introduce additional protections for incompetent persons.

From a legal point of view, an adult is presumed to have capacity, unless the contrary is proved. Moreover a person may have the capacity to make one decision even if they lack capacity to make another. In addition, as the Nuffield Council of Bioethics stated regarding people with dementia, "in many cases, it will be very clear whether a person with dementia does or does not have the capacity to make a particular decision. However, there will be times when the person's ability to make a particular decision will be difficult to determine" (Nuffield Council of Bioethics, 2009. P xxii). Something similar may happens with patients suffering from other psychiatric disorders.

Regarding patients with **neuropsychiatric** disorders , the judgment of incompetence is in fact an especially difficult task. A diagnosis of a psychiatric disorder or dementia does, in itself, not mean that the subject is not able to understand and to express valid informed consent: clinical experience and empirical studies (Dunn *et al*., 2006) show that a number of patients with Alzheimer's disease, schizophrenia or depression are able to understand, appreciate, reason and express a valid choice when asked to take part in a research project. However, even when these mentioned **intellectual** abilities are present, sometimes, **according to Tan et al. (2003),** patients with psychiatric disorders may have beliefs and values that can **raise questions about their competence and the full adequacy of tools for assessment to capture elements that are relevant to competence**. To perform an accurate assessment of competence in the medical context, it is

essential to consider the capacity to perform a very specific act, such as choosing a given treatment or deciding to enrol in a well-defined research project. In the case of genetic research and biobank participation, the competence assessment should therefore not aim to evaluate the patient's competence in general terms but should evaluate competence in a single task.

In this context, we consider the use of specific instruments to assess patients' understanding, **appreciation and reasoning, coupled with tailored evaluation of subjective believes and values relevant to** competence useful to formulate a judgment with the aim of respecting and promoting subjects' autonomy when they are able to express their informed consent and also to protect them when they are unable to give their consent (Nicholson *et al.*, 2008). Criteria for non-competent adults should therefore not be applied on the basis of a diagnosis but should be applied only after a medical judgment of incompetence has been formulated in relation to genetic research and biobank participation, **taking into consideration also the possibility of borderline cases where a person' capacity is uncertain**.

Requirement for a subject's representative

In the event of collection, storage and use of samples belonging to incompetent subjects, the intervention of a third person to give consent on the behalf of the incompetent person is required **by the majority of analyzed guidelines.** Nevertheless, **from the one hand the** identification of the representative can be difficult **and, from the other one, this solution does not meet the needs of people with uncertain capacity.** Two national guidelines (8, 17) refer to the consultation of carers or relatives even though they are not qualified as legal representatives. The other guidelines suggest that the legally authorized representative is the person suitable to give consent in lieu of the incapacitated adult. The identification of the authorized representative therefore depends on

national legislation that may vary from one country to another and may involve procedures with different degrees of complexity.

A major distinction can be drawn between countries that have and have not enacted *ad hoc* statutes dealing with biomedical research involving incompetent adults. For instance, overseas, Section 24178 of the California Health and Safety Code (effective in 2003) provides a list of subjects able to give surrogate informed consent that starts with the "agent pursuant to an advance health care directive" (California Health and Safety Code Section, 2003). On the European side, in the United Kingdom, the Mental Capacity Act (MCA), adopted by the British Parliament in 2005, has a proper section dedicated to research with people who lack capacity. The Law Commission in drafting the Mental Capacity Act has followed the Medical Research Council recommendations on the topic and states that a person engaged in caring for the person who lacks capacity or is interested in his/her welfare has to be consulted (Mental Capacity Act, 2005). In Belgium, the law on patients' rights of 2002 gives a clear ranking of legal representatives (Law on the rights of patients, 2002).

On the contrary, there are countries that do not have a specific law regarding the involvement of incapable adults in biomedical research, and therefore general rules provided by the national legal system for people not able to decide on behalf of themselves apply (Pascalev and Vidalis, 2010). For example, this is the case in Italy where the legal representative (*tutore* or *amministratore di sostegno*) has to be appointed by the Court in a case-by-case manner in compliance with the rules of the Italian Civil Code. In these situations, it is unrealistic to imagine a representative being appointed solely for the subject's inclusion in a biobank.

Moreover and importantly, consent on the behalf of the interested person is not an acceptable solution, because it mortifies subjects' possibility to express autonomy, for people in the "grey

zone" where judgement of capacity is difficult and capacity is uncertain. Both for situations, as Italy, where it is impracticable to appoint a legal representative just for a subject' inclusion in a research project, and for people in the "grey zone" we regard as important the involvement of a family member. The possibility that a family member could serve as a proxy, even if not appointed by the judge as representative, needs to be discussed at least at the local level involving both the scientific and the ethics committees of the biobank. Indeed, from an ethical point of view, the most important requirement for a patient's representative is that the representative has shared time and experiences with the patient in the past and also has a close relationship in the present so that the representative is able to give voice to the patient's wishes and have patient's wellbeing as his/her first concern. **For people with uncertain or variable capacity a "joint decision making with trusted family members" might help bridge the gap between the time when a person with dementia is fully able to make their own decisions, and the time when formal proxy decision making becomes necessary on a regular basis (Nuffield Council of Bioethics, 2009); and between periods of stronger or weaker manifestation of symptoms of psychiatric disorders.** ~~This seems to be very much in line with the growing phenomenon of patients' rights, which are intended both as a political/legal acknowledgement (European patients' forum, 2009) and as a claim from patients' associations, which, in the case of neuropsychiatric patients, are often the claims of family members (for the Italian situation: Associazione italiana malattia di Alzheimer; Alzheimer Italia).~~

Decision making process

With regard to decision making processes involving subjects not able to give consent, the classic work by Brock and Buchanan (Brock and Buchanan, 1989) identifies three guiding principles: the

respect of advance directives (expressed in a living will or entrusted to a person); the substitute judgment of a person close to the patient who "puts him/herself in the place of the patient"; and the best interest of the subject.

The two principles of best interest and respect of subjects' previous wishes are explicitly mentioned as criteria for decision making in 5 and 3 of the considered guidelines respectively, while substitute judgment is the criterion of one of the guidelines. The other guidelines do not suggest criteria and leave the decision of how to act to the representative.

All of the mentioned criteria have some criticisms. Empirical studies show that there is little concordance between the judgments of the substitute and the person concerned (Ditto *et al.*, 2001; Emanuel and Emanuel, 1992). The best-interest criterion – unless interpreted in an extensive manner as in the Mental Capacity Act- risks projecting the values of others onto the subject, particularly when it is applied by a physician or a researcher rather than a carer/relative. The advance directives cannot include all the possible biomedical situations.

Just like the Italian Society of Neurology bioethics group (Defanti *et al.*, 2007), **in patients who have been previously competent,** we regard advance directives particularly valuable and effective if they include an appointment of a trusted person who can contribute to making decisions in the context of current medical/scientific possibilities, on the basis of the indications given by a patient, and on the basis of his/her values and past life. **Advance directives may cover every aspect of cure and research related to the subject's health, and the use of biological materials for purpose of research may be part of the discussion between the subject and the trusted person.** ~~Nevertheless, in this very specific case we are considering a problem may persist because it is quite difficult to determine what decision the person would have made about the use of his/her~~

~~biological materials for purpose of research, given the matter is not currently a common object of discussion.~~

In the situation of subjects with uncertain capacity, the best expression of their autonomy would be promoted through the involvement of family members or close friends who can support patients' decision, taking into consideration their past and present wishes.

Principles of non-therapeutic research

Minimal risk, benefit for others, benefit for the participant, and the impossibility of achieving knowledge through other means are the fundamental principles for non-therapeutic research on incapable adults.

Among those principles, minimal risk is the most difficult to define in research on biological materials, given the specific type of the entailed risk. In contrast to common biomedical research in which enrolled subjects run a physical risk, and the discussion focuses on the definition of what a *minimal* risk is, the issue at stake in research involving biobanks consists of the definition of risk itself. In fact, the collection of human biological materials, usually a sample of blood, for purposes of genetic research and storage in a biobank does not entail any significant risk of physical harm. Nevertheless, the challenge with the low risk argument in biobank research is that it misses the specific character of this kind of research, where the main risk is not physical but is related to information (Hofmann, 2009) that could be obtained from the collected samples and that cannot be fully foreseen at the moment of the collection. Information is also related to issues of privacy breaches, stigmatisation and discrimination based on genetic makeup (Hens *et al.*, 2009; WonPat-Borja *et al.*, 2012).

We consider that the evaluation of the risk in the absence of a benefit for the donor should follow the scientific evaluation of the possibility of achieving the knowledge without the involvement of neuropsychiatric subjects who are unable to give consent; **while people with uncertain capacity should not be prevented in their altruistic wish to contribute to scientific enterprise**. ~~Furthermore, given that the type and amount of information coming from the samples cannot be fully foreseen at the moment of collection, every effort should be made to guarantee patients' privacy while simultaneously ensuring that a plan for communicating results is in place; this communication is expected to be especially complicated because of those subjects' impaired capacity. Indeed, although research studies on biological materials are conducted for investigative purposes, and no interesting personal result nor direct benefit for the donor are expected as immediate outcomes of the research, the possibility of some meaningful personal information – unexpected or later in time - cannot be excluded. Both rules for privacy protection and a plan to communicate results should be an explicit part of any biobank regulation (Porteri and Borry, 2008).~~

The role of the ethics committee

The majority of guidelines containing provisions on incompetent adults require the ethics committee's evaluation as an additional guarantee for research on human biological materials. **Even though ECs should be asked for opinion about every kind of research project involving the use of biological materials, we regard as important to stress the point when dealing with the** enrolment of persons with neuropsychiatric disorders. **The ECs** involvement aims at guaranteeing not only that the research project is scientifically and ethically sound in general terms and that patients are not exposed to unjustifiable risks, but also that every effort to respect the patient's

autonomy and wishes has been made (Alzheimer's Association, 2004). In this sense, ethics committees should require research protocols and biobank regulations to describe the planned informed consent process - i.e. the methods and instruments used to assess patients' competence, the presence of an independent evaluator of competence and an independent auditor of the informed consent process, the method used to identify patients' representatives, and the value given to advance directives expressed by patients when they were fully competent. Lastly, members of research ethics committees might also personally supervise the enrolment of patients (Porteri *et al.*, 2009).

CONCLUSION

We **analyzed and discussed** papers and guidelines dealing with the participation of incompetent adults in genetic research and biobanks **with a focus on** research situations involving patients suffering from psychiatric disorders and dementia. **We therefore suggested some measures to implement guidelines taking into considerations those patients' specificity. First, we suggested that the judgement of competence should be made not on the base of a diagnosis nor in general terms but with reference to the very specific task of deciding participation in a biobank and genetic research; instruments for competence assessment can be useful to formulate a judgement with the double aim of promoting subjects' autonomy and protecting patients not able to give consent. Second, we underlined the circumstance that people with neuropsychiatric disorders might have uncertain and variable capacity that requires patients be given additional support to respect as much as possible their possibility to express autonomy; joint decisions with family members or close friends can be a good solution. Third, in case of subjects non able to give consent, advance directives are a valuable mean to respect patients' previous wishes and**

feelings regarding participation in research. Fourth, given the non-therapeutic character of genetic research, patients not able to give consent should not be included in research if knowledge can be differently achieved; while people with uncertain capacity should not be prevented in their altruistic wish. ~~Plan to communicate meaningful personal results, although generally not expected in biobank research, should be put in place.~~ Fifth, in order to guarantee that patients' autonomy and wishes are respected and promoted, ethics committees should require that research protocols describe the planned informed consent process, including elements on patients' competence assessment, family members' involvement, representative identification, respect of patients' previous wishes.

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Conflict of interest

None declared.

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N	Year	Guideline Title	Guideline Developer	Scope	Website
1	1995	Human Tissue Ethical and Legal Issues	Nuffield Council on Bioethics	United Kingdom	http://www.nuffieldbioethics.org/sites/default/files/Human%20tissue.pdf
3	1998	E-2.07 Clinical Investigation	American Medical Association	United States of America	http://www.ama-assn.org//ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion207.page
5	2000	Guidelines for genetic register and associated genetic material	National Health and Medical Research Council	Australia	http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e14.pdf
8	2001	Human Tissue and Biological Samples for Use in Research – operational and ethical guidelines	Medical Research Council	United Kingdom	http://bioetica.org/umsa/fuentes/UK.%20Medical%20Research%20Council.%20Human%20Tissue%20and%20Biological%20Samples%20for%20use%20in%20Research.%20Operational%20and%20Ethical%20guidelines.pdf
10	2002	International Ethical Guidelines for Biomedical Research Involving Human Subjects	Council for International Organizations of Medical Sciences (CIOMS)	International	http://www.cioms.ch/publications/layout_guide2002.pdf
13	2002	Human Tissue Research	Bioethics Advisory Committee Singapore	Singapore	http://research.singhealth.com.sg/PDF/SingHealthTissueRepository/HumanTissueResearchConsultation27Feb2002.pdf
14	2002	Inside Information Balancing interests in the use of personal genetic data	Human Genetic Commission (HGC)	United Kingdom	http://www.who.int/genomics/elsi/regulatory_data/region/euro/036/en/index.html
16	2003	Avis : Les enjeux éthiques des banques d'information génétique : pour un encadrement démocratique et responsable	Commission de l'éthique de la science et de la technologie	Canada	http://www.ethique.gouv.qc.ca/fr/assets/documents/big/BanquesdinformationGenetique_avis2003_fr.pdf

17	2003	Ethical issues raised by collections of biological material and associated information data: "biobanks", biolibraries"	National Consultative Ethics Committee for Health and Life Sciences	France	http://ec.europa.eu/research/biosociety/pdf/opinion_77.pdf
18	2003	International declaration on human genetic data	United Nations Educational, Scientific and Cultural Organization (UNESCO)	International	http://portal.unesco.org/en/ev.php-URL_ID=17720&URL_DO=DO_TOPIC&URL_SECTION=201.html
19	2003	Genetic databases. Assessing the benefits and the impact on human and patient rights	World Health Organization (WHO)	International	http://www2.law.ed.ac.uk/ahrc/files/69_lauriewhoreportgeneticdatabases03.pdf
20	2004	DNA Banking and Personal Data in Biomedical Research: Technical, Social, and Ethical Questions	German Society of Human Genetics	Germany	http://www.medgenetik.de/sonderdruck/en/DNA%20Banking_engl_060605.pdf
21	2004	Biobanks for research	Nationaler Ethikrat	Germany	http://ec.europa.eu/research/biosociety/pdf/ethikrat_opinion_biobanks.pdf
22	2005	Human Biological Material: recommendations for collection, use and storage in research	Irish Council for Bioethics	Irleand	http://irishpatients.ie/news/wp-content/uploads/2012/04/Irish-Council-of-Bio-Ethics-BiologicalMaterial1.pdf
25	2006	Biobanks: obtainment, preservation and utilization of human biological material. Medical-ethical guidelines and recommendations	Swiss Academy of Medical Science	Switzerland	http://www.google.it/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CDcQFjAB&url=http%3A%2F%2Fwww.samw.ch%2Fdms%2Fen%2FEthics%2FGuidelines%2FCurrently-valid-guidelines%2Fe_RL_Biobanken.pdf&ei=9xwwUs28OYTNswapjIH4Aw&usg=AFQjCNGC5VM2c0QmhZZZxiVnvbbFyefC-g&bvm=bv.51773540,d.Yms

26	2007	Biobanks for medical research	Austrian Bioethics Commission	Austria	http://www.bundeskanzleramt.at/DocView.axd?CobId=25510
27	2007	Bioethics Guidelines on human studies	The European Nutrigenomics Organization (NuGO)	Europe	http://nugo.dife.de/bot/files/NUGO-Bioethics-Guidelines-on-Human-Studies.pdf
29	2009	Guidelines on Human Biobanks and Genetic Research Databases	Organisation for Economic Co-operation and Development (OECD)	Europe	http://www.oecd.org/sti/biotech/44054609.pdf

Tab. 1 Guidelines referring to adults not able to give consent

Issues	Arguments / Positions	
Informed consent	Who should give consent	Representative identified in accordance with the law (3,5,10,13,16,18,19,21,22,25,26,27)
		Trustworthy person (17); carer or relative (8)
	How the representative should act	Best interest (7,8,17,18,20)
		Natural and previous wishes (21,26,27)
		Reasonable to volunteer (3)
	What the role of the incompetent person is	Consent in relation to capacity (10,16,22)
		Respect of refusal (1,10,16,21,26,27)
Principle of non-therapeutic research	Minimal risk (1,8,10,19,21,22)	
	Benefit for others (10,16,19,21,22)	
	Benefit for the participant (8,10,16,19,21)	
	Knowledge cannot be otherwise obtained (1,3,10,22)	
Ethics committee review	Explicitly required (1,8,10,13,20,26)	
	Indirectly required (5,7,14,19,21,22,27)	

Tab. 2 Content analysis of the guidelines: main topics and arguments / positions